REMARKS

Claims 11-16 and 18-28 are pending prior to entry of this Amendment. Claims 11-14, 16, 18-23, and 25-28 have been withdrawn from consideration. By way of this Amendment, no claims have been amended, claims 29-33 have been newly added, and claims 11-14, 16, 18-23, and 25-28 have been canceled. Support for the newly added claims is provided by the originally-filed national stage claims and the originally-filed claims from the corresponding international application. No new matter has been added.

Restriction

The application stands restricted to the subject matter presented as Group III in the Restriction Requirement of March 24, 2008, currently represented by claims 15 and 24. Claims 11-14, 16, 18-23, and 25-28 have been withdrawn from consideration and are canceled herein without prejudice to any subsequently filed divisional application(s).

Title

The title of the application has been amended.

Rejections under 35 USC 103

Claims 15 and 24 stand rejected under 35 USC 103 as being obvious over Almarsson '293 in view of Staniforth WO'694, Muller-Walz WO'671, and Keller WO'979. The Examiner claims that combination of the references renders the claimed invention obvious. However, a close review reveals the failure of the references, alone or in combination, to teach or suggest the claimed method of inhibiting chemical degradation of an active ingredient.

US 6,559,293 (Almarsson et al)

Almarsson identifies the problem solved by the instant invention. That is, the reference recognizes that suitability of particular excipients may depend on the specific active ingredients in a dosage form. In particular, Almarsson provides a general teaching that lactose or water may have a detrimental effect on primary and secondary amine active ingredients:

> *"The suitability of a particular excipient may also depend on the specific active ingredients in the dosage form. For example, the decomposition of some active ingredients can be accelerated by some*

excipients such as lactose, or when exposed to water. Actives ingredients that comprise primary and secondary amines are particularly susceptible to such accelerated decomposition." col. 17, lines 15-21.

The teachings of Almarsson correspond with the background provided by Applicant in the instant application. See page 1, line 31 to page 2, line 3. Thus, Almarsson simply restates the problem solved by Applicant.

Almarsson provides no teaching or suggestion that degradation of an active ingredient in the presence of a carrier, such as lactose, can be ameliorated by use of calcium stearate. If anything, Almarsson teaches away from the use of calcium stearate by specifically referring to antioxidants such ascorbic acid, pH buffers, or salt buffers as compounds that reduce the rate by which an active ingredient will decompose (col. 17, lines 22-32).

WO 2001/078694 (Staniforth et al)

Staniforth is concerned with formulations for inhalation to the lung and, more specifically, with the use of additive materials to promote the release of active ingredient particles from carrier particles.

Staniforth speaks generally of a wide range of potential additive materials (p. 14, l. 25 to p. 19, l. 10). The reference expresses a particular preference for amino acid additive materials (page 16 lines 17-18), but also mentions (Example 12) that calcium stearate may be used (see p38, lines 22-25 and p40).

While Staniforth suggests that an additive material limits the interaction of the active ingredient and the carrier molecule by occupying all of the high energy sites on the carrier particle, there is nothing in the Staniforth reference to suggest that any of the additive materials would have the effect of inhibiting chemical degradation of an active ingredient. Further, there is nothing in the reference that would lead one of skill in the art to single out calcium stearate from the laundry list of other additive materials listed in the reference.

WO 02/078671 (Muller-Walz), and corresponding U.S. Application 10/473874

Muller-Walz relates to the use of various salts, including calcium stearate, in suspension aerosol formulations based on hydrofluoroalkane propellants. The salts are said to improve the suspension stability, the mechanical function of the dosing valve, the

dosing precision, and the chemical stability of an active substance suspended in hydrofluoroalkane propellant. (p. 6, ll. 3-9)

Muller-Walz is non-analogous to the instant application since, the principal problem addressed by the reference is stability of the aerosol suspension, not the stability of the active ingredient itself. (p. 5, para at l. 15) The reference does mention that salts "can also improve the chemical stability of the pharmaceutical active compound, in particular the moisture resistance of moisture-sensitive active compounds." (p. 6, ll. 24-30), but the comment is made in the context of aerosol formulations and does not address interactions with carriers such as lactose.

In contrast to the aerosol formulation of Muller-Walz in which moisture is thought to cause degradation of an active compound, the present application relates to formulations in which degradation of active ingredient substances is caused, at least in part, by interaction with a carrier, such as lactose. There is nothing in the Muller-Walz reference that would suggest to one of skill in the art that calcium stearate would be effective in inhibiting chemical degradation brought about by interaction with such a carrier as opposed to chemical instability due to moisture.

WO 00/28979 (Keller et al), and English equivalent U.S. Pat. No. 6,645,466

Keller is directed to improvement of moisture resistance of dry powder formulations. More specifically, Keller relates to the influence of moisture on the fine particle dose (FPD) during the storage of an inhalation powder. Keller provides no teaching with regard to chemical degradation of an active compound, much less the use of calcium stearate to prevent such degradation.

Summary

In summary, it is Applicant's understanding that the Examiner has provided references that demonstrate:

- •lactose may degrade an active ingredient substance (Almarsson),
- •calcium stearate helps an active ingredient physically release from a lactose carrier (Staniforth),
- •calcium stearate improves suspension stability of an active ingredient in an aerosol formulation (Muller-Walz),
- •may protect an active from moisture (Muller-Walz), and
- •magnesium stearate improves the fine particle dose of dry powder formulations exposed to moisture (Keller).

After review of the references, all that has been provided are the disjointed teachings regarding physical interactions of active ingredients and lactose, moisture resistance, and aerosol suspension stability. The references, alone or in combination, simply fail to teach or suggest Applicant's claimed method of inhibiting chemical degradation of an active ingredient substance.

Despite the failure of the references to teach or suggest the invention, the Office maintains that the invention is obvious. In order to make the obviousness rejection, the Office asserts (page 6 of the Office Action) that "any agent which minimized interaction between a primary and secondary amine containing compound formulated with lactose or provided moisture resistance would protect the primary and secondary amine containing compound from chemical degradation.".

The correlation of minimized interaction, or moisture resistance, with inhibition of chemical degradation is unsupported by the references, and such assertion is improper without adequate support (see MPEP 2144.03). Applicant requests that support be provided for the Office's assertion.

Since the conclusion of obviousness is unsupported by the references, as demonstrated above, Applicant submits that the rejection under 35 USC 103 should be withdrawn, and such action is respectfully requested.

Double Patenting

Claim 15 has been provisionally rejected on the grounds of obviousness-type double patenting in view of U.S. Application 10/564191 after combination with a variety of references. Applicant respectfully requests that this provisional rejection be deferred until either this application or the '191 application is found to allowable.

Conclusion

Applicant asserts that the instant Amendment places the application in a condition for allowance, and such allowance is respectfully requested.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge any fees or credit any overpayment, particularly including any fees required under 37 CFR Sect 1.16 or 1.17, and any necessary extension of time fees, to deposit Account No. 07-1392. The Examiner is invited to contact the undersigned at (919) 483-8160, to discuss this case, if desired.

Respectfully submitted,

J. Scott Young
Attorney for Applicants
Reg. No. 45,582

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GlaxoSmithKline Inc.
Five Moore Drive, PO Box 13398
Research Triangle Park, NC 27709
(919) 483-8160
fax: (919) 483-7988
Scott.S.Young@GSK.com